THE BIOLOGY OF GROWTH

A Review of its Place in Heredity and Evolution

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HERE is a collection of five lectures* which were delivered in 1925-6 by members of the staff of the University of Missouri, in an attempt to present a comprehensive concept of growth. While each lecture contains matters of interest, they are not all equal in value. A symposium of this kind cannot be expected to show that cohesion which is usually looked for in a book, but which a course of lectures by different persons need not necessarily achieve. Furthermore, when delivered in the form of lectures to stimulate curiosity and to focus attention, the subject matter under review is excellent, but it appears a trifle thin when cast into book form.

Certain matters have been omitted which might reasonably be expected to occupy a place in an elementary exposition of the phenomena of growth. One of these is the detail of the growth of the uterus of a pregnant mammal, which is effected by increase in size and not in number of the cells which compose the uterine wall; the subsequent involution of the uterus after birth takes place by reduction of the size of the cells. This important case serves as a warning that growth and cell-multiplication are not necessarily synonymous. When dealing with nutritional requirements, an interesting point which might be mentioned is (as Osborne, Mendel, and Ferry showed in 1912) that that constituent of protein known as lysine, which is essential for growth, can be synthesized (or substituted for) in the body of an adult mammal suckling its young from a diet which is deficient in lysine. Such a diet is, however, insufficient for growth if administered direct to the young animals themselves.

Another important piece of work which might have profitably been included is that of Drew (1923). This investigator observed that if tissues of an adult animal are allowed to decompose at the temperature of the body (i.e., to undergo autolysis), they furnish a substance which has remarkable powers of promoting growth when administered to tissues growing *in vitro*. Further, this effect is very similar to that which is produced by an extract of a cancerous tumour. The more malignant (i.e., rapid-growing) the tumour, the more effective is its extract. It would appear then that cancerous tissue differs from healthy tissue in that it possesses continuous supplies of this growth-promoting substance, whereas healthy tissue possesses it only when and as it is damaged. It is further probable that this autolysed extract plays a part in the normal process of repair of the body, when damaged tissue is made good by the growth of other tissue to take its place.

The description of the pineal gland as being situated " at the base of the brain " is a little misleading, and the physico-chemical postulates in the form of a catechism are hardly illuminating. With regard to the first of these : " Why does growth occur? Because there is an inherent tendency, or force, which causes cells to divide," Gray (1927) has shown that there is probably no fundamental association between growth and cell-division. These two processes are the factors which determine the size of individual cells. In some cases they may establish a well-defined equilibrium, but in others not. At all events, the authors exerted

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caution in not referring to the remarkable work of Gurwitsch (1926) on the cell-multiplying effect of certain physical rays which were supposed by him to be produced by certain living tissues. Fortunately, this caution may be relaxed, now that the essentials of Gurwitsch's results have been confirmed by Reiter and Gábor (1928).

The book has, however, an unfortunate demerit in that, although published in 1928, it does not take account of the results of studies on growth which appeared in the preceding three years from the work of a number of investigators, chiefly on this side of the Atlantic. As the study of growth has itself grown very rapidly during these years, it is regrettable that the opportunity was lost of presenting an up-to-date account of it. The new results are certainly not as widely known as they deserve to be, and advantage will therefore be taken of this opportunity for bringing them succinctly to notice.

The late Dr. T. S. P. Strangeways, who devoted so much of his life to the investigation of problems of growth in tissue-culture, was led to conclude (1924) that the tendencies of a cell to multiply and to become specialized and differentiated were more or less mutually exclusive. This important view is all the more significant when considered in the light of Drew's (1923) experiments, in which he obtained the re-differentiation of the structure of the tubes of the kidney or of a mammary gland from sheets of tissue which were dividing rapidly and had lost their previous differentiation. The re-differentiation was induced by adding connective tissue to the culture. This result is in full accordance with that of Champy (1914), who found that epithelium and connective tissue grow only very little when they are present in a culture together, but as soon as the connective tissue dies the epithelium loses its differentiation and grows rapidly.

Turning now to the raw materials which an embryo uses when it grows and differentiates, Needham (1926a) has shown in the case of the chick that carbohydrates are made use of first, then proteins, and lastly fats are laid under contribution as sources of energy. Further, he has shown (1926b) that the selection of the kind of material which an embryo uses as a source of energy at a given moment is made by factors residing within the embryo, and is independent of the supplies of the various materials available. The succession : carbohydrate—protein—fat, is of great interest from several points of view, which Needham discusses (1926c and 1927c). It is the order of : ascending calorific value, descending degree of intramolecular oxygenation, attack by digestive ferments in the intestinal tract of higher animals, decreasing solubility in water, decomposition during autolysis, simplicity of synthesis by solar energy, etc., and Needham is inclined to ascribe a phylogenetic significance to it.

There is no relation between the periods of maximum combustion of proteins and fats and the periods of the maximum absorption of these two classes of foodstuffs (Needham, 1927a), but there does appear to be a relation of this kind in the case of the combustion and absorption of carbohydrates (1927b). The nature of the material which is absorbed during any given period is probably controlled by variations in the permeability to water-soluble and to fat-soluble substances of the cells of the blood-vessels of the blastoderm. Further work indicates that in the building up of the embryo, molecules of protein are brought into the body of the embryo intact, and are there broken down before being re-formed into its own characteristic protein molecules.

The developing chick presents the very interesting phenomenon of the "foie transitoire" in the cells of the yolk-sac, which regulate metabolism until the embryo's liver is sufficiently well formed to take on this function for itself (1927b). The yolk-sac of the chick is in this respect analogous and indeed perhaps homologous to the placental chorion of the mammal. Lastly, Needham (1927d) has examined the degree of efficiency with which the yolk and white of the egg are converted into the flesh and blood of the chick.

GROWTH OF CANCEROUS CELLS

No mention of sources of energy during growth would be complete without reference to Warburg's (1926) important results derived from experiments on the respiration of healthy and of cancerous cells. Whatever the material from which energy is derived, a healthy tissue obtains energy by burning the raw material with oxygen : the process known as aerobic respiration. A cancerous tissue, however, obtains its energy by splitting up the molecule of raw material by fermentation. So sugar is broken down to lactic acid by the process known as glycolysis, and no oxygen is required for this process. Obtaining energy by these means is accordingly called anaerobic respiration. Healthy tissues can obtain energy by glycolysis when they are deprived of oxygen, but they respire aerobically when oxygen is available, and glycolysis then ceases. But a cancerous tissue will continue to obtain energy by glycolysis, however much oxygen is supplied to it, and the more malignant the tumour is, the more energy does it derive from glycolysis. A cancerous cell therefore differs from a healthy cell in that its power of aerobic respiration is damaged or destroyed.

While dealing with energy-sources, those who are attracted by general rules with remarkable exceptions to them will be interested in the fact that the amount of energy (number of calories) which is necessary to double the weight of the new-born of all mammalian species investigated is proportionally the same for all, except for man : 4,808 calories are required to make 1 kg. of normal body, except by man, who requires six times as much (Rubner, 1908).

Gray (1926, 1928a, and 1928b) has carried out a number of investigations into the growth of fish, and has been led to some conclusions of great importance regarding the attempts which have been made to "explain" the growth of an animal by means of a mathematical formula or equation. He has shown (1929) that, when the growth of an organism is plotted in the form of a curve, that curve can always be represented by more than one equation within the limits of probable error in the taking of measurements. When more than one type of cell is present, as is always the case in all animals above the Protozoa, growth-curves are insufficient for the construction of the real equation on which the processes of growth are based. It is therefore futile to expect to be able to "obtain the laws of growth" simply by a consideration of curves.

Of a different nature are the results of Huxley's (1924a) re-investigation of certain phenomena, and his discovery that in a number of cases in which an organ grows relatively faster than the rest of the body, the differential growth-rate is constant during long periods and is susceptible of interpretation by a mathematical formula. (This formula is $y=bx^k$, where x is the body, y is the organ in question, k is a constant usually about 1.5, and b is a constant of proportion.)

DIFFERENTIAL GROWTH

Without going into the causes of constant differential growth-rates (which remain obscure), attention may be paid to a number of interesting and important consequences which result from them. An organ or part which grows at a constant differential rate when compared with that of the rest of the body is called a heterogonic organ. Such an organ is the abdomen in female crabs, which in them is wider than in the males; for, while in the former it is heterogonic, its growth in the latter is proportional to that of the rest of the body, or isogonic. Females of the so-called fiddler-crab are found with a narrow abdomen, and this has hitherto been taken to imply that in these individuals there has been a qualitative change towards maleness. Huxley (1924b) has made it clear that the phenomenon is merely one of quantitative reduction in the relative growth-rate (i.e., in the constant k) of a heterogonic organ.

It has been known for some time that male earwigs may be of one of two types : either "high" with large caudal pincers, or "low" with small ones, and the distinction between them has hitherto been ascribed to a difference in the factors inherited by the individuals of one or the other type. Huxley (1927a) has made it clear that the difference is not one of heredity but of development, for there are two "equilibrium-positions" into which the degree of development of the pincers fall. The effect of an increase in the size of the body is the transference of an increasing number of individuals from the "low" to the "high" equilibrium-position. A similar phenomenon is observable in respect of the size of the horn in the beetle *Xylotrupes* (Huxley, 1927b).

These results are of considerable general importance, for they show that the distinctions between "high" and "low" forms of certain insects, which have hitherto been considered to be of taxonomic importance, have no basis whatever as a means of classification (Huxley, 1927c).

EVOLUTION IN A STRAIGHT LINE

Another aspect of the work on constant differential growth-rates has an important bearing on the phenomenon which is usually known as orthogenesis in evolution. When a lineage of animals is considered, it is often found that a certain variation (such as the development of horns or antlers on the head, for instance) becomes progressively accentuated, as if evolution were taking place along a straight line in a definite direction. It is now plain (Huxley, 1924a) that this result will be achieved if the variation in question involves a heterogonic organ, and if the size of the body enlarges. This enlargement of the body can in many cases be actually shown to have taken place (as in that of the fossil *Titanotheres*), and in the case of deer, the relative antler-size rises steadily with absolute body-size (Huxley, 1926).

The orthogenetic accentuation of the heterogonic organ is therefore nothing more nor less than a correlated variation. Why the size of the body should increase during evolution it is not easy to say, but it is known that several factors, both internal and external (such as glands of internal secretion, temperature, etc.), are concerned in it, and in many normal environments selection is exerted in favour of larger size. At all events, this explanation of orthogenesis has lifted the latter conception out of the category of mystical fancies on to the level of a genetical and physiological problem.

It is of interest to note that the mathematically predictable size of a heterogonic organ appears to be a maximum limiting value, as is shown by the fact that in crabs the claws (heterogonic in the male) can temporarily become reduced below this value, as can the width of the abdomen in female crabs (in which it is heterogonic). It is quite possible that this limiting value may be found to be due to some simple geometrical relation, such as that of an area increasing isogonically to an area remaining stationary, as Bidder (1925a) has suggested.

Now, the heterogonic organs in male crabs, the claws, are made up of a number of joints, and if the relative sizes of the joints are compared, it is found that the heterogony is more pronounced in some joints than in others (Huxley, 1927c). These facts lead to the following important conclusion: since (i) the proportion of size of organ to size of body varies at different absolute sizes of the body if the organ is heterogonic; and (ii) the proportion of the parts of the organ also vary *inter se* at different absolute sizes—therefore species of animals with heterogonic organs *have no constant specific shape*.

It is a remarkable thing that the joint of the claw of the male crab which grows fastest is not the terminal joint, but the penultimate one; and similarly the portion of the abdomen in which the growth is relatively the greatest is near the hind end, as Miss Shaw (1928) has shown. These regions may therefore be regarded as growth-centres.

Another remarkable feature is that the growth of the heterogonic claw appears to affect the growth of the limbs in the adjacent segments. In most crabs and lobsters the large claw is on the first walking limb, and it is found that, when compared with the size of those of the female, in the male the second to fifth walking limbs are larger, and the limb just in front of the claw (the third maxilliped) is smaller. Further, in

Palæmon carcinus, the claw is on the second walking limb, and here it is the third to fifth walking limbs which are larger in the male than in the female, and the first walking limb is smaller (Huxley and Tazelaar, 1929).

THE LIMITS OF GROWTH

If studies on heterogonic growth show that specificity of shape is not invariably to be found in a species, other considerations show that specificity of size in a species is not universal either. Bidder (1925b) has pointed out that, as a rule, aquatic animals grow throughout life and have no fixed final adult size. This power of perpetual growth cannot, however, be possessed by terrestrial or aerial animals without involving a disturbance of physical and mechanical relations of the animal with its environment, as a result of which the animal's life would be impossible. As Haldane (1927) shows, the size of an animal living on land cannot increase beyond a certain value, for in the process of enlargement the weight of the body increases faster than, and outstrips the increase in, the strength of the legs. A size is reached at which the legs will not support the body. To take another example : since insects breathe by means of blind tubes, the length of tube which permits a minimum essential renewal of oxygen is limited. This factor, therefore, limits the maximum size to which insects can aspire.

In a similar way, it can be shown, as Hesse (1924) points out, that warm-blooded animals cannot live in cold climates unless they are of large size. The larger the animal, the smaller is the ratio of its surface to its volume. As heat is lost by radiation from the surface, a large animal has a heat-loss which is low relatively to its size. Heat-loss is made up for by combustion, and the fuel is obtained by eating. A small warm-blooded animal living in a cold climate has a heat-loss so large relatively to its size that, in order to make up for it, it would require to consume more food than it would have time to eat.

The examples here considered show how important is the control of the size of animals during evolution, so that it should transgress neither maximum nor minimum limiting values. Should this occur, the animal would become extinct, and this is probably the field in which the explanation of the extinction of a number of fossil animals of monstrous size is to be sought. The factors concerned in this connection, however, only act indirectly in their control of growth, by killing off the animals which have grown too much or too little for their particular mode of life. It remains to consider the factors which act directly by controlling and limiting growth during development.

THE HEREDITARY FACTORS

Of these factors there is unfortunately little to say. It is, however, clear that the limitation of growth in development has its hereditary as well as its embryological aspect. Concerning the latter, mention must be made of Hesse's (1927) demonstration of the fact that for each type of structure of an animal and for any given area of the internal surface of its gut, there is a maximum size of the body which cannot be exceeded owing to limitation of raw material digested. With regard to the hereditary limitation of growth, it is obvious that some factor must be transmitted from parent to offspring which brings it about that in identical environments Pekingese are invariably smaller than St. Bernards. Robb (1929), who has investigated the growth of giant and of dwarf races of rabbits, has shown that the percentage growth-rate is identical for both from birth to puberty, but the dwarfs are only half the size of the giants at birth. The greater size of the giants is therefore due to a more rapid uterine growth.

The study of the factors which control growth is one of the most important in biology, in plants as well as in animals, and reference must be made to the admirable summary by Pràt and Malkovský (1927) of the state of knowledge as regards growth from a botanical aspect. But the study of growth is no less fundamental in eugenic science. The hereditary aspect as reflected in the inheritance of the most suitable size for a given environment; the embryological aspect, concerned with problems of nutrition and infantile environment; and the pathological aspect, dealing with endocrine disorders, and, most serious of all, with tumours; all these must form the foundation of that knowledge which is the prerequisite to any attempt at applying it in the control of any species, whether domestic plant or animal, or pest, or man.

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